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THE PATENTS ACT, 1970

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IT IS HEREBY CERTIFIED THAT, the annex is a true copy of
Application and Complete specification filed on 30.09.2002 in respect
of Patent Application No. 847/MUM/2002 of Sun Pharmaceutical
Industries Ltd, Acme Plaza, Andheri-Kurla Road, Andheri(E)
Mumbai-400 059, India, an Indian Company.

This certificate is issued under the powers vested on me under
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..... Dated this 10th day of February 2003

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(N.K. GARG)

ASST CONTROLLER OF PATENTS & DESIGNS

Dmg
(Pharm)
NP

FORM 1

**THE PATENTS ACT, 1970
(39 OF 1970)**

**APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)**

Com 18-1
8m
30-09-02

We, **SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA**

AN INDIAN COMPANY

hereby declare -

- (i) that we are in possession of an invention titled **"PROCESS FOR PURIFICATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE"**
- (ii) that the complete specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) Dr. Kilaru Srinivasu 2) Dr. Thennati Rajamannar; of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

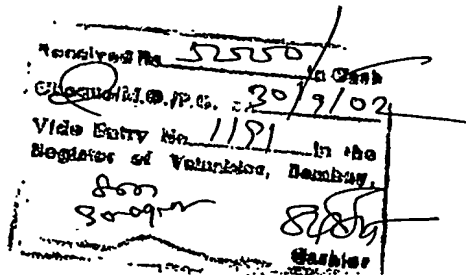
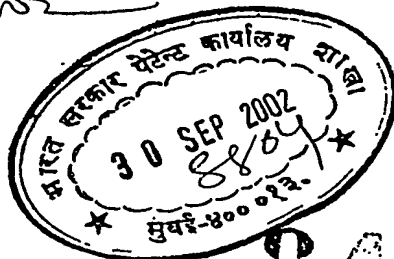
That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

**Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212110.**

847/MUM/2002

30/9/2002



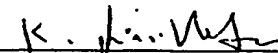
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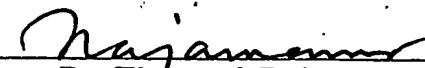
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MUM

Following declaration was given by the inventors-
We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 24th day of September, 2002.

(Signatures)

1. 
Dr. Kilaru Srinivasu

2. 
Dr. Thennati Rajamannar

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

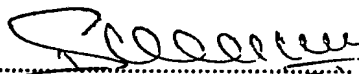
Following are the attachment with the application:

- 1) Complete specification (3 copies)
- 2) Fee Rs. 5000 in cheque bearing No. 333670 dated 15.05.02 on Bank of Baroda.

We request that a patent may be granted to us for the said invention

Dated this 24th day of September, 2002.

(Signature)



DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To

The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

**THE PATENTS ACT, 1970
(39 OF 1970)**

**COMPLETE SPECIFICATION
(See section 10)**

**PROCESS FOR PURIFICATION OF 1-[3-(DIMETHYLAMINO) PROPYL] -1-(4-
FLUOROPHENYL)-1,3-DIHYDRO-5- ISOBENZOFURAN CARBONITRILE**

SUN PHARMACEUTICAL INDUSTRIES LTD.

**A company incorporated under the laws of India having their office at ACME PLAZA,
ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA,
INDIA**

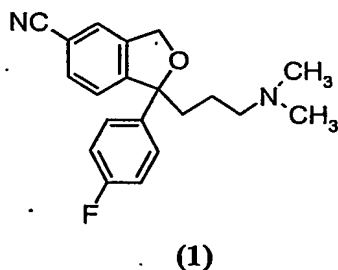
**The following specification particularly describes and ascertains the nature
of this invention and the manner in which it is to be performed.**

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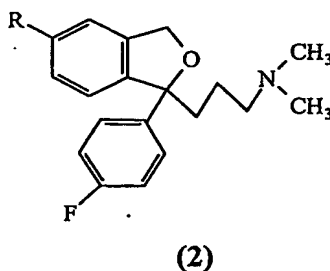
PROCESS FOR PURIFICATION OF 1-[3-(DIMETHYLAMINO)PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE

The present invention relates to purification of the base of well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of Formula (1) by removal of polar and non-polar impurities.



INTRODUCTION

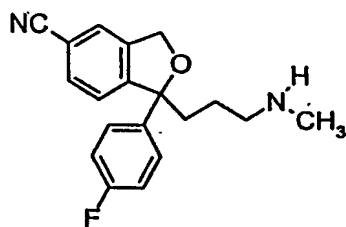
United States Patent No. 4,136,193 (Indian reference not available, hereinafter referred to as '193) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. It discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5- substituted derivatives, compounds of Formula (2) wherein R is halogen or trifluoromethyl, by reaction with cyanide source.



The cyanide exchange process as illustrated in example 2 of '193 patent involves reaction of compound of formula (2) with cupro cyanide in dimethylformamide by refluxing for 4 hours, followed by work-up of the reaction mixture to get the crude citalopram base. In the work-up of the reaction the organic phase is washed with 10% sodium cyanide solution,

treated with activated carbon, the resultant oil dissolved in ether and extracted with 20% aqueous acetic acid and the aqueous phase neutralized with NaOH solution and extracted in ether, dehydrated and treated with active carbon and vacuum evaporated to obtain citalopram base as an oil.

The cyanide exchange process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile has been reported (PCT application WO 0145483) to give the desmethylcitalopram, a compound of formula (3) and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.



(3)

Subsequently several other patents appeared in the literature regarding enriching crude citalopram base or salt purity so as to obtain pharmaceutically acceptable base or acid addition salts.

BACKGROUND OF THE INVENTION

Several other patents for newer synthetic methods have also been reported in the literature for making citalopram as given under, for which Indian references are not available-

1. Conversion 5-amido or ester group to a 5-cyano group (WO 9819513)
2. Conversion 5-amino group to a 5-Cyano group (WO 9819512)
3. Conversion 5-formyl group to a 5-Cyano group (WO 9930548)
4. Conversion 5-oxazolinyll or thiazolinyll group to a 5-Cyano group (WO 0023431)

5. Conversion 5-halo group to a 5-Cyano group (WO 0011926)
6. Conversion 5-halo group to a 5-Cyano group (WO 0013648)

GB patent 2359811 (Indian reference not available) discloses the purification method for citalopram wherein, the desmethyl impurity is removed by reacting with an agent which converts the desmethyl impurity into an amide or amide like neutral derivative which subsequently can be removed by means of simple operations like acid base treatment.

The end product obtained by the process of GB 2359811 and other above-mentioned prior art processes is crude citalopram in an oil form. The prior art patents do not teach any method for purifying the base further to obtain crystalline base of citalopram.

In general the processes described generates many of the side products, which needs to be removed in order to make pharmaceutically acceptable product. The PCT application WO 0013648 (equivalent of United States Patent Application US 2002/0077353 A1) states that the exchange of 5-bromo group to 5-cyano is not very convenient in commercial scale, since the yield was rather low, the product was impure and in particular that it was very difficult to separate the resulting citalopram from the corresponding 5-bromo compound.

The reissued United States Patent RE 34712 describes synthesis of crystalline citalopram base in example 3, starting from a racemic diol via a methanesulfonyl ester in dichloromethane. The reaction mixture was washed with 0.1M NaOH solution twice, the organic phase separated, dried and evaporated to obtain a crystalline citalopram base.

PCT application WO 01/02383 (Indian reference not available) relates to a process for preparation of citalopram via an aldehyde intermediate. The text teaches that citalopram obtained in the form of oil can be crystallized to obtain pure product by dissolution in isopropanol, followed by crystallization. However, the removal of polar and non-polar impurities in a single crystallization step is not disclosed.

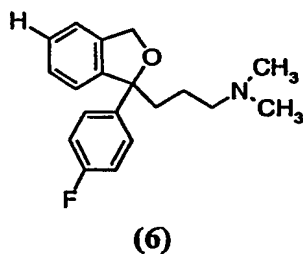
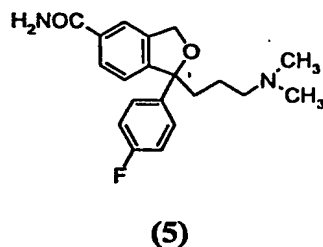
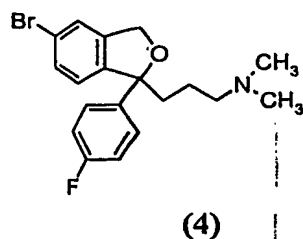
PCT application WO 01/68627 (equivalent United States Patent Application US 2001/0031784 A1, Indian reference not available) describes a process for purification of citalopram base to obtain 99.8% w/w pure, preferably more than 99.9% w/w pure crystalline base. As can be seen from example 1 of WO 01/68627, the citalopram HBr is suspended in water and toluene, neutralized by addition of NaOH, phases are separated and organic phase is washed with water and filtered. The volatiles are removed in vacuum and the obtained citalopram base that is still in an oil form is crystallized from n-Heptane. In all the worked out examples the crystalline base is obtained starting from a citalopram salt or the salt which is being formed *in-situ*, making the process laborious. The patent teaches use of an aprotic solvent for crystallisation, such as an alkane, including n-heptane, hexane and isooctane, and high and low boiling petroleum ethers and substituted aromates, including toluene and xylenes. In all the worked out examples n-heptane has been employed.

None of the relevant prior art methods provide a crystallization process, which in a single step yields crystalline citalopram base by simultaneous removal of polar and non-polar impurities. Also no prior art reference teaches the use of a combination of solvents for simultaneous removal of the polar and non-polar impurities in a single crystallization step.

OBJECT OF THE PRESENT INVENTION

We have observed that the use of hydrocarbon solvents to remove a mixture of impurities consisting polar and non-polar components from crude citalopram base was not efficient.

The object of the present invention is to remove the polar and non-polar impurities using one solvent system either by using pure solvent or solvent mixture consisting of more than one solvent. Known processes for preparation of citalopram yield, citalopram that may contain both polar and non-polar impurities, for example, the process as in example 2 of US patent 4,136,193 yields citalopram with major impurities that include, the starting 5-bromo compound, viz., [1-(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-bromoisobenzofuran, a compound of Formula (4); an amide, viz., [1-(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carboxylic acid amide, a compound of Formula (5); desmethyl citalopram, viz., [1-(3-Methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, a compound of Formula (3); descyanocitalopram, viz., [1-(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, a compound of Formula (6) and high molecular weight impurities. Hereinafter the impurities (3), (4), (5) and (6) will be referred to as desmethyl, 5-bromo, amide and descyano compounds, respectively.



These impurities are brought down to an extent of less than 1% individually by any of the known prior art methods. It has been observed that the removal of non-polar impurities like starting material (4), descyano citalopram (6) are possible using hydrocarbon solvents, however the polar impurities like amide (5) and desmethyl citalopram (3) are difficult to eliminate upon treatment with hydrocarbon solvents.

SUMMARY OF THE PRESENT INVENTION

The present invention provides a process for removal of both polar and non-polar impurities from citalopram base.

Particularly the present invention provides a process for purification of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of Formula (1), comprising crystallizing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from a solvent system,

wherein the solvent system comprises a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof.

DETAILED DESCRIPTION OF THE INVENTION

In order to develop a purification method to eliminate both nonpolar and polar impurities we have investigated the use of various solvents like aliphatic linear, branched and cyclic and aromatic hydrocarbons or solvents like esters, nitriles, ethers, ketones and alcohol and found that the method is not satisfactory either in terms of overall purity or yield. But the use of a solvent system comprising of a first solvent, which is a hydrocarbon solvent in combination with a second solvent such as alcohols, esters, ethers, ketones was found to be advantageous.

Table I gives the % reduction in impurities, viz., desmethyl (3), 5-bromo compound (4), amide (5) and descyano (6), when the citalopram base is purified according to the process of the present invention comprising crystallization of the citalopram base from the solvent system comprising, a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof. In the purification process of the present invention, the use of a solvent system comprising a first solvent, which is a hydrocarbon solvent in combination with a second solvent selected from esters, ethers and ketones afforded the selective removal of nonpolar impurities viz., 5-bromo compound (4) and descyano (6) effectively and the use of hydrocarbon solvents with alcohols as second solvent eliminated both non-polar and polar impurities viz., 5-bromo compound (4), descyano (6), desmethyl (3) and amide (5) impurities to the required level.

The process of the present invention may be carried out by heating the citalopram base, a compound of formula (1), that is to be purified in a solvent system comprising a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof, followed by cooling to allow for crystallization of citalopram base. The citalopram base of HPLC purity greater than 99% may be obtained by process of present invention. The base of citalopram obtained by the process of the present invention may be further converted to a pharmaceutically acceptable acid addition salt, preferably the hydrobromide salt. The citalopram hydrobromide of HPLC purity greater than 99.5% may be obtained by converting the citalopram base obtained by the process of the present invention to the hydrobromide salt in a conventional manner.

The base of compound of formula (1), which is to be subjected to purification may be the base obtained from a crude salt of citalopram or from a crude mixture comprising the base of citalopram. The crude salt may be any convenient salt such as the hydrobromide, hydrochloride, sulphate, oxalate, phosphate, nitrate or any other convenient salts.

The terms crude salt and crude mixture refers to the fact that the salt and the mixture, respectively, comprise impurities, which must be removed. The crude salt or base may be a salt or base separated directly from the reaction mixture, or it may have been subjected to some initial purification, e.g. recrystallization, treatment with activated carbon or silica gel. The salt or the base may be prepared by any of the above-mentioned prior art processes. The salt might be obtained directly by the reaction or it may be formed subsequently by reaction of citalopram base with an acid.

The second solvent may be selected from the group consisting of alcohols, esters, ketones, ethers or mixtures thereof.

The % solvent ratio of first solvent: second solvent that can be employed for the purification ranges between 95:5 to 60:40, the more preferred range being 95:5 to 75:25 and most preferred being 95:5 to 80:20, respectively.

In a preferred embodiment of the present invention the % solvent ratio of first solvent: second solvent is 90:10, respectively.

The hydrocarbon solvents as the first solvents that can be employed are linear, branched, cyclic and aromatic hydrocarbons. Examples of hydrocarbon solvents include pentane, hexane, heptane, 3-methyl hexane, 3-methyl heptane, isooctane, cyclohexane, cycloheptane, methylcyclohexane. The preferred being cyclic aliphatic hydrocarbons of C5 to C12 carbon atoms, more preferably C5 to C7 such as cyclohexane and cycloheptane and the most preferred being cyclohexane.

Examples of aromatic hydrocarbon solvents that can be used include benzene, toluene, xylenes, preferred being toluene and xylenes, most preferred being toluene.

In the case of alcohol as second solvent, alcohols having C1 to C10 carbons of linear, branched and cyclic alcohols, which are of primary, secondary and tertiary in nature can be employed. Examples of alcoholic solvents include methanol, ethanol, n-propanol, n-butanol, isopropanol, isobutanol, sec-butanol, t-butanol, cyclopentanol, cyclohexanol,

benzyl alcohol. The preferred being C1 to C5 alcohols of primary and secondary in nature such as methanol, ethanol, n-propanol, n-butanol, isopropanol, isobutanol; more preferred being n-propanol, n-butanol and isopropanol and most preferred being n-propanol.

The second solvents like esters, ketones and ethers are preferably C1 to C5 solvents.

Examples of esters include methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, sec-butyl acetate, tertiary butyl acetate, preferred being ethyl acetate, isopropyl acetate, butyl acetate and most preferred being ethyl acetate.

Examples of ketones include acetone, ethylmethyl ketone, methylisobutyl ketone, cyclohexyl methyl ketone, preferred being acetone, ethylmethyl ketone and most preferred is acetone.

Examples of ethers include diethylether, diisopropylether, tertiary butylmethylether, preferred being diethylether, tertiary butylmethylether and most preferred is diethylether.

The temperature at which the process of the present invention can be carried out is in the range between 40°C to 150°C, preferably 40°C to 100°C more preferably 50°C to 80°C and most preferably 60°C to 80°C.

In a preferred embodiment of the present invention the solvent system employed for purification of the compound of formula (1), comprises cyclohexane:n-propanol in a % solvent ratio of 90:10, respectively.

The following examples are given by way of illustration only and not to be construed as limiting.

Example 1)

20.0 g of crude 1-(3-Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile (purity 97.3%) is taken in a mixture of cyclohexane (80 ml) and n-propanol (8 ml) and heated to 60-65° C to get clear solution and cooled to 5-10°C, the product precipitated was filtered and dried at 40-45° C under vacuum. (HPLC purity >99.0%)

Example 2)

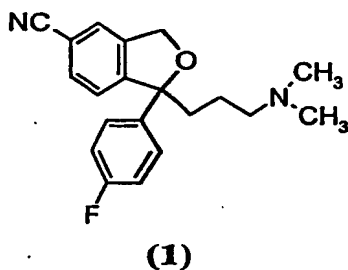
The citalopram base obtained as in example 1 is converted to citalopram hydrobromide in isopropanol in a conventional manner. The citalopram hydrobromide obtained is dissolved in acetone, charcolised and concentrated to obtain citalopram hydrobromide (HPLC purity >99.5%).

Table I

Solvents	% Solvent Ratio Hydrocarbon solvent: Second solvent	% reduction of the impurities			
		Des cyano (6)	Amide (5)	Starting material (4)	Des methyl (3)
n-Heptane	100:0	70	0	63	12
n-Heptane : n-Propanol	90:10	72	35	69	45
Cyclohexane: n-Propanol	90:10	100	70	75	70
Cyclohexane: Isopropanol	90:10	100	48	75	25
Cyclohexane: n-Butanol	90:10	88	48	69	29
Cyclohexane: Ethyl acetate	90:10	100	0	74	17
Cyclohexane: Acetone	90:10	88	18	66	20
Cyclohexane: Diethyl ether	90:10	86	9	17	13

We claim

- 1) A process for purification of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of Formula (1), comprising crystallizing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from a solvent system,



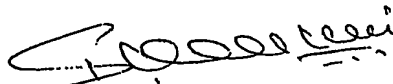
- wherein the solvent system comprises a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof.
- 2) The process as claimed in claim 1, wherein the hydrocarbon solvent is a linear, branched, cyclic aliphatic or aromatic solvent.
 - 3) The process as claimed in claim 2, wherein the cyclic aliphatic hydrocarbon solvent is a solvent containing C5 to C12 carbon atom.
 - 4) The process as claimed in claim 3, wherein the cyclic aliphatic hydrocarbon solvent is cyclohexane.
 - 5) The process as claimed in claim 1, wherein the second solvent is selected from a group consisting of ester, ether, ketone or mixture thereof.
 - 6) The process as claimed in claim 1, wherein the second solvent is an alcohol.

- 7) The process as claimed in claim 6, wherein the alcohol is a primary alcohol containing C1 to C5 carbon atom.
- 8) The process as claimed in claim 7, wherein the alcohol is n-propanol.
- 9) The process as claimed in claim 6, wherein the alcohol is isopropanol.
- 10) The process as claimed in claim 1, characterised in that the % solvent ratio of the first solvent to the second solvent is between the range of 95:5 to 60:40.
- 11) The process as claimed in claim 1, characterised in that the % solvent ratio of the first solvent to the second solvent is between the range of 95:5 to 75:25.
- 12) The process as claimed in claim 1, characterised in that the % solvent ratio of the first solvent to the second solvent is between the range of 95:5 to 80:20.
- 13) A process as claimed in claim 1, wherein the % solvent ratio of the first solvent to the second solvent is 90:10.
- 14) The process as claimed in claim 13, wherein the first solvent is cyclohexane.
- 15) The process as claimed in claim 14, wherein the second solvent is n-propanol.
- 16) The process as claimed in claim 14, wherein the second solvent is isopropanol.
- 17) The process as claimed in claim 14, wherein the second solvent is ethyl acetate.
- 18) The process as claimed in claim 14, wherein the second solvent is diethylether.
- 19) The process as claimed in claim 14, wherein the second solvent is acetone.

- 20) A process as claimed in claim 1 wherein the solvent system containing the compound of formula (1) is heated at a temperature between the range of 40°C to 150°C.
- 21) A process as claimed in claim 20, wherein the temperature is between the range of 50°C to 80°C.
- 22) A process as claimed in claim 21, wherein the temperature is between the range of 60°C to 80°C.
- 23) The process as claimed in claim 1, wherein the solvent system contains cyclohexane as the first solvent and n-propanol as the second solvent in a % solvent ratio of 90:10, respectively, and the solvent system is heated at a temperature between 60°C to 70°C.
- 24) The process as claimed in claim 13 wherein the solvent system is heated at a temperature between 60°C to 70°C.
- 25) The process as claimed in claim 1, wherein 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of Formula (1) is obtained with HPLC purity greater than 99%.
- 26) The process as claimed in claim 1, wherein 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of Formula (1) is further converted to its hydrobromide salt.
- 27) The process as claimed in claim 26, wherein the citalopram hydrobromide having HPLC purity greater than 99.5% is obtained.
- 28) A process as claimed in claims 1 to 25, substantially as herein described and illustrated in example 1.

29) A process as claimed in claim 26 or 27, substantially as herein described and illustrated in example 1 and 2.

Dated this 27th day of September, 2002.



**DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED**

ABSTRACT

The present invention provides a process for purification of, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, by removal of polar and non-polar impurities.

To

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